REMARKS

The Examiner has indicated that the amendments submitted on June 4, 2002, and September 26, 2002 have been entered. The Examiner indicates that Claims 14 and 17-32 are pending. Applicants respectfully submit that Claims 14 and 26-28 have already been cancelled (*See*, Appendix I and page 5 of the Office Action Response mailed May 20, 2002). However, in order to ensure that these Claims have indeed been cancelled without prejudice, Applicants hereby request that they be cancelled.

Applicants appreciate the Examiner's statement that the previous 35 USC §112, second paragraph rejection of Claim 23 has been withdrawn. However, Claim 24 is rejected under 35 USC §112, second paragraph, as allegedly being indefinite. In particular, the Examiner indicates that recitation of "the protein" lacks antecedent basis. Applicants have amended Claim 24, in order to provide the correct antecedent basis.

In addition, the Examiner has objected to Claims 24-25, as allegedly being of improper dependent form for failing to further limit the previous Claim. In particular, the Examiner indicates that in Claim 24, the term "protease" is broader than "microbial subtilisin" in Claim 23. In regards to Claim 25, the Examiner indicates that "subtilisin" is broader than "microbial subtilisin" in Claim 23. Applicants have cancelled Claims 24 and 25, without prejudice in order to further the prosecution of the present application and Applicants' business interests. Applicants reserve the right to pursue the originally filed, similar and/or broader Claims in the future.

Further, the Examiner has indicated that should Claims 14 and 26-28 be found allowable, Claims 29-32 will be objected to under 37 CFR §1.75,I as being a substantial duplicate thereof. Applicants respectfully submit that Claims 14 and 26-28 have already been cancelled (*See*, Appendix I and page 5 of the Office Action Response mailed May 20, 2002). However, in order to ensure that these Claims have indeed been cancelled without prejudice, Applicants hereby request that they be cancelled.

Applicants appreciate the withdrawal of the previous 35 U.S.C. §112, first paragraph with respect to the presence of new matter in Claim 18. However, the Examiner has rejected Claims 14, 17-19, and 26-32, under 35 USC §112, first paragraph, as allegedly not meeting the written description requirement. The Examiner also indicates that Claim 17 allegedly contains new matter in step (b), and Claim 18 contains new matter in step (a)(I). The Examiner argues that the recitation of "at least

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one cytokine" cannot be found in the disclosure. The Examiner states that the use of particular species of cytokines in Example 1 does not support the generic use of "at least one cytokine" as recited in Claims 17 and 18. Applicants have amended these Claims to remove the recitation of at least one cytokine. Applicants respectfully submit that the pending Claims are novel and unobvious over the art previously cited by the Examiner, as indicated in the Office Action Response mailed May 20, 2002. Applicants believe that there is nothing in the cited art that would lead one of ordinary skill in the art to perform the steps of the pending Claims. As the Specification as filed clearly supports the use of differentiated dendritic cells (*See e.g.*, page 5, line 23-24; page 9, line 30; page 26, lines 1-8) in the methods of the present invention, Applicants respectfully submit that the Claims are allowable.

Applicants appreciate the Examiner's removal of the prior rejection of the Claims under 35 USC §112, first paragraph, as well as the removal of the prior art rejection of the Claims.

CONCLUSION

In light of the above remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-5838.

Respectfully submitted,

Date: 7 March 2003

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APPENDIX I

MARKED-UP VERSION OF REWRITTEN, ADDED, AND/OR CANCELLED CLAIMS

The following is a marked-up version of the Claims, pursuant to 37 C.F.R. §1.121 (c)(1)(ii), with instructions and markings showing changes made herein to the previous version of record of the Specification and Claims. Underlining denotes added text while bracketing denotes deleted text.

Please cancel Claims 14, 24-28.

Please amend the Claims as follows:

17. (Twice Amended) A method for determining a T-cell epitope of a peptide, comprising the steps of:

(a) obtaining from a single human blood source a solution of dendritic cells and a solution of naïve CD4+ and/or CD8+ T-cells;

(b) differentiating said dendritic cells[, wherein said differentiating comprises combining said dendritic cells with at least one cytokine];

(c) combining said solution of differentiated dendritic cells and said naïve CD4+ and/or CD8+ T-cells with the peptide, said peptide comprising said T-cell epitope; and

(d) measuring proliferation of said T-cells in said step (c).

18. (Twice Amended) A method of reducing the allergenicity of a protein comprising the steps of:

(a) identifying a T-cell epitope in said protein by

(i) contacting an adherent monocyte-derived dendritic cell that has been differentiated [by exposure to at least one cytokine *in vitro*,] with a peptide comprising said T-cell epitope; and

(ii) contacting said dendritic cell and peptide with a naïve T-cell, wherein said naïve T-cell has been obtained from the same source as said adherent monocyte-derived dendritic cell, and whereby said T-cell proliferates in response to said peptide; and

(b) modifying said protein to neutralize said T-cell epitope such that the modified protein induces less than or substantially equal the baseline proliferation of said naïve T-cells.

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APPENDIX II
CLEAN VERSION OF THE ENTIRE SET OF PENDING CLAIMS AS AMENDED IN THIS COMMUNICATION

The following is a list of the Claims as they would appear following entry of this amendment.

17. (Twice Amended) A method for determining a T-cell epitope of a peptide, comprising the steps of:

(a) obtaining from a single human blood source a solution of dendritic cells and a solution of naïve CD4+ and/or CD8+ T-cells;

(b) differentiating said dendritic cells,;

(c) combining said solution of differentiated dendritic cells and said naïve CD4+ and/or CD8+ T-cells with the peptide, said peptide comprising said T-cell epitope; and

(d) measuring proliferation of said T-cells in said step (c).

18. (Amended) A method of reducing the allergenicity of a protein comprising the steps of:

(a) identifying a T-cell epitope in said protein by

(i) contacting an adherent monocyte-derived dendritic cell that has been differentiated, with a peptide comprising said T-cell epitope; and

(ii) contacting said dendritic cell and peptide with a naïve T-cell, wherein said naïve T-cell has been obtained from the same source as said adherent monocyte-derived dendritic cell, and whereby said T-cell proliferates in response to said peptide; and

(b) modifying said protein to neutralize said T-cell epitope such that the modified protein induces less than or substantially equal the baseline proliferation of said naïve T-cells.

19. The method according to claim 18, wherein the protein is a protease.

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20. (Amended) A method for reducing the allergenicity of a microbial subtilisin comprising the steps of:

(a) determining a T-cell epitope of said subtilisin comprising (i) obtaining from a from a single human blood source a solution of dendritic cells and a solution of naïve CD4+ and/or CD8+ T-cells; (ii) promoting differentiation in said solution of dendritic cells; combining said solution of differentiated dendritic cells and said naïve CD4+ and/or CD8+ T-cells with peptide fragments of said subtilisin; and (iv) measuring proliferation of said T-cells in said step (iii); and

(b) modifying the peptide which includes the T-cell epitope to neutralize said epitope.

21. The method according to claim 20, wherein the microbial subtilisin is derived from a *Bacillus*.

22. The method according to claim 21, wherein the *Bacillus* is selected from the group consisting of *B. lentus, B. subtilisin, B. amyloliquefaciens* and *B. licheniformis*.

23. (Amended) The method according to claim 20, wherein said epitope of said microbial subtilisin is modified by: (a) substituting the amino acid sequence of the epitope with an analogous sequence from a human homolog of said microbial subtilisin; (b) substituting the amino acid sequence of the epitope with an analogous sequence from a non-human homolog of said microbial subtilisin; or (c) substituting the amino acid sequence of the epitope with a sequence which substantially mimics the major tertiary structure attributes of the epitope.

29. The method according to claim 18, wherein said T-cell epitope is modified by a substitution selected from the group consisting of:

(a) substituting the amino acid sequence of said T-cell epitope with an analogous sequence from a human homolog to the protein of interest;

(b) substituting the amino acid sequence of said T-cell epitope with an analogous sequence from a non-human homolog to the protein of interest; or

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(c) substituting the amino acid sequence of said T-cell epitope with a sequence which substantially mimics the major tertiary structure attributes of the epitope.

30. The method according to claim 29, wherein said T-cell epitope is modified by substituting the amino acid sequence of the T-cell epitope with an analogous sequence from a human homolog to the protein of interest.

31. The method according to claim 29, wherein said T-cell epitope is modified by substituting the amino acid sequence of said T-cell epitope with an analogous sequence from a non-human homolog to the protein of interest.

32. The method according to claim 29, wherein said T-cell epitope is modified by substituting the amino acid sequence of the epitope with a sequence which substantially mimics the major tertiary structure attributes of said T-cell epitope.

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